REMARKS

Claims 1-8 and 21-34 are pending in the application, claims 9-20 having been cancelled without prejudice. New claims 21-34 have been added. Support for the new claims can be found in the specification at, e.g., page 7, line 34, to page 8, line 14; page 9, line 35, to page 10, line 1; page 26, line 28, to page 27, line 7; page 27, lines 28-35; page 38, lines 2-5; and page 38, lines 13-16. No new matter has been added by these amendments.

Objection to the Specification

On page 2 of the Office Action, the Examiner objected to the missing ATCC deposit numbers at, e.g., pages 8 and 29-32 of the specification. The blank spaces in the specification are intended to allow for the insertion of information related to the deposit of biological materials. Upon the indication of allowable subject matter, applicant will either provide the relevant deposit information or delete the blank spaces.

Rejections Under 35 U.S.C. §101 and 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1-8 as allegedly lacking utility. In a related rejection, the Examiner rejected claims 1-8 as allegedly not enabled. According to the Examiner,

> [t]he claimed polypeptides are not supported by a specific asserted utility and do not, without further research and experimentation, provide an immediate benefit to the public. While the specification asserts that the claimed polypeptides (CARD-14) are useful as modulating agents in regulating a variety of cellular processes including cell growth and cell death (see the specification at page 4, lines 35-36) and in treating diseases associated with apoptosis, any actual or practical benefit to the public (to one of ordinary skill in the art) is speculative. The specification discloses a plethora of diseases associated with an undesirably low or high rate of apoptosis, as well as numerous inflammatory diseases, which theoretically could be modulated by CARD-14 (see page 5, line 12, through page 6, line 32). The asserted utility of treating disease therefore lacks specificity. There is no basis in the specification upon which to conclude that *any* of the polypeptides encompassed by the claims are, or will turn out to be, therapeutic for any diseases after testing.

Applicant respectfully traverses the rejection in light of the following comments.

The present application describes the characterization of CARD-14, a novel caspase recruitment domain (CARD)-containing protein. The CARD domain is a protein-binding module that mediates the assembly of CARD-containing proteins into apoptosis and NF-kB signaling complexes. CARD-14 has an N-terminal CARD domain, a central coiled-coil domain, and a C-terminal tripartite domain containing a PDZ domain, an Src homology 3 domain, and a GUK domain with homology to guanylate kinase (see specification at page 24, line 20).

The application as filed includes extensive working examples that characterize the role of CARD-14 in cell signaling pathways involved in apoptosis and/or inflammation. In particular, applicant has demonstrated that: (1) CARD-14 selectively binds to the CARD of Bcl-10, a signaling protein that activates NF-kB through the IkB kinase complex in response to upstream stimuli (page 20, line 9, to page 22, line 9); (2) CARD-14 induces phosphorylation of Bcl-10 (page 22, line 11, to page 23, line 20); and (3) CARD-14 stimulates the activation of NF-kB (page 23, line 22, to page 24, line 15). These findings, which indicate that CARD-14 functions as an upstream activator of Bcl-10 and NF-kB signaling, are also detailed in the enclosed publication of Bertin et al. (2001) J. Biol. Chem. 276(15):11877-82 ("Exhibit A").

Bcl-10 is a well-characterized pro-apoptotic protein containing an N-terminal CARD domain and a C-terminal effector domain that mediates activation of NF-kB (see, e.g., Koseki et al. (1999) *J. Biol. Chem.* 274:9955-61; Yan et al. (1999) *J. Biol. Chem.* 274:10287-92; Thome et al. (1999) *J. Biol. Chem.* 274:9962-68; Srinivasula et al. (1999) *J. Biol. Chem.* 274:17946-54)). Bcl-10 activates NF-kB by acting upstream of NIK and IkB kinase (Srinivasula et al., *supra*). Bcl-10 activity has been implicated in B cell lymphomas of mucosa-associated lymphoid tissue.

NF-kB is a transcription factor that is expressed in many cell types and activates genes that have NF-kB sites in their promoters. Molecules that regulate NF-kB activation play critical roles in both apoptosis and in the stress-response of cells. With respect to stress-response, NF-kB activates genes that control immune defense mechanisms and inflammation. NF-kB and the NF-kB pathway have specifically been implicated in mediating chronic inflammation in inflammatory diseases such as asthma, ulcerative colitis, and rheumatoid arthritis (Barnes (1997) *New England Journal of Medicine* 336:1066).

As detailed herein, (i) the NF-kB signaling pathway is involved in a variety of inflammatory responses, and (ii) Bcl-10 activates NF-kB signaling pathways and apoptosis.

Furthermore, applicant has demonstrated that CARD-14 is a CARD-containing protein that binds to Bcl-10, induces phosphorylation of Bcl-10, and induces NF-kB activity. Accordingly, the claimed CARD-14 polypeptides are useful in screening assays for identifying compounds that can be used to regulate NF-kB activity, apoptosis, and/or inflammation. In particular, applicant's discoveries identify CARD-14 as a useful target for screening for potential therapeutics for treating inflammatory disorders and/or disorders associated with inappropriate levels of apoptosis. For example, CARD-14 polypeptides can be used to screen for compounds that inhibit or enhance CARD-14 activity. Such compounds are expected to be candidate therapeutic compounds for the regulation of cell growth and death.

The specification discloses that the claimed polypeptides can be used in screening assays and provides extensive teachings on methods of screening for and identifying compounds that modulate CARD-14 activity (see, e.g., page 66, line 28, to page 75, line 23). For example, the specification describes screening to identify molecules that prevent the dimerization of CARD-14 and screening to identify molecules that block the binding of Bcl-10 to CARD-14 (see, e.g., page 67, lines 3-8). Such screening assays can employ full-length CARD-14, a variant of CARD-14 having an appropriate biological activity, or a portion of CARD-14, e.g., the CARD domain. Candidate test compounds that can be used in such screens include, but are not limited to, peptides, peptidomimetics, and small molecules (see, e.g., page 66, line 29, to page 67, line 2).

The present lack of utility rejection is based largely upon the Examiner's assertion that there is "no basis in the specification upon which to conclude that *any* of the polypeptides encompassed by the claims are, or will turn out to be, therapeutic for any diseases after testing." Such a therapeutic use is only one of several utilities for the claimed polypeptides asserted in the application. Although applicant submits that the claimed polypeptides can be used for therapeutic applications, the comments provided herein demonstrate that the claimed polypeptides can also be used to screen for compounds that modulate CARD-14 activity.

To meet the statutory requirements for utility and enablement, applicant must demonstrate a use for the claimed composition and teach one of ordinary skill in the art how to make and use the claimed composition without resort to undue experimentation. Accordingly, irrespective of whether the claimed polypeptides can themselves be used as therapeutics, the

utility of the claimed invention is clearly established by applicant's demonstration that the polypeptides can be used in screening assays to identify compounds that regulate NF-kB activity, apoptosis, and/or inflammation.

At page 3 of the Office Action, the Examiner stated that "many research tools such as telescopes, gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility" (emphasis added). Consistent with the Examiner's comments, the claimed polypeptides have a specific, credible and substantial utility in that they can be used in screening assays to identify compounds that regulate CARD-14 activity. In such screening assays, the claimed polypeptides are clearly not "the subject of basic research, whose usefulness or lack thereof has yet to be established." Rather, applicant has clearly established the importance of CARD-14 in biological pathways that regulate NF-kB activity, apoptosis, and/or inflammation. It is for this reason that the claimed polypeptides have a utility in carrying out screens to identify compounds that can modulates these processes. Such screens are intended to arrive at a particular result (identify potential therapeutics) rather than to investigate the usefulness of the claimed polypeptides.

In view of the forgoing, the claimed polypeptides have a specific, credible and substantial utility. Accordingly, applicant respectfully requests that the Examiner withdraw the rejections under 35 U.S.C. §101 and 35 U.S.C. §112.

35 U.S.C. §112, First Paragraph (Enablement)

Claims 1-8 were rejected as allegedly not enabled. At page 5 of the Office Action, the Examiner stated that "[g]iven the teachings found in the art that therapeutic efficacy for any of the caspases has not yet been determined or developed, detailed guidance is required in the specification to enable one of skill in the art to be able to use the claimed polypeptides." In addition, the Examiner stated that "[t]here is no guidance [in the specification] as to how to administer any CARD-14 polypeptides for treatment of any specific disease. There are no working examples directed to the administration of CARD-14 polypeptides for treatment of any disease." In light of these comments, the Examiner concluded that it would require undue experimentation for one of skill in the art to use the claimed polypeptides to treat disease.

Applicant respectfully traverses the rejection in light of the following comments.

The teachings of the specification, combined with the knowledge of a person of ordinary skill in the art at the time the present application was filed, enable a skilled artisan to use the claimed polypeptides. As detailed above with respect to the lack of utility application, applicant need only enable a single use of the claimed invention. Even if the Examiner questions whether the claimed polypeptides can themselves be used as therapeutics, as asserted by applicant, the specification clearly enables the use of the polypeptides to carry out screens to identify compounds that modulate CARD-14 activity. As provided by MPEP § 2164.01(c),

> when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use. If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention. (emphasis added)

In light of applicant's findings demonstrating the biological activities of the CARD-14 protein, applicant submits that one of ordinary skill in the art would have been able, at the time of filing of the present application, to use the claimed polypeptides without undue experimentation, e.g., in screening assays to identify candidate therapeutic agents.

In support of the enablement rejection, the Examiner stated that Thornberry et al. (1998) Science 281:1312-1316 ("Thornberry") teaches "that the ability to administer caspases for therapeutic benefit is not within the realm of present day medicine, but that extensive research and development is needed to better understand the role of the caspases and to determine whether they can be used as therapeutics."

First, Thornberry does not mention the possibility of administering caspases as therapeutics. Instead, Thornberry discusses a variety of possible therapies that involve either the inhibition or activation of caspases (page 1316).

Second, as noted above, therapeutic use is not the only utility of the claimed polypeptides. The polypeptides are also useful for screening for candidate therapeutic compounds that modulate the biological activity of CARD-14. Thus, far more relevant is Thornberry's statement that "[c]aspases are attractive potential targets for the treatment of these conditions [neurodegenerative diseases, ischemia-reperfusion injury, graft-versus-host disease,

and autoimmune disorders] because of the requisite role of these enzymes in apoptosis and the appealing prospect of small-molecule inhibitor therapy" (page 1316). A small-molecule inhibitor of the sort described by Thornberry is precisely the sort of compound that can be identified by carrying out a screening assay using the claimed polypeptides (see specification at page 66, lines 29-33, describing using small molecules in CARD-14 screening assays). Thornberry nowhere suggests that *screening* for compounds that modulate caspase activity is not useful. To the contrary, Thornberry indicates that the identification of small molecule inhibitors constitutes an important means for developing therapeutics to treat a variety of diseases. Accordingly, Thornberry supports the assertions in the specification that the claimed polypeptides are useful in screening assays to identify compounds that modulate CARD-14 activity.

In light of these comments, applicant submits that one of ordinary skill in the art would have been able, at the filing of the present application, to use the claimed polypeptides without undue experimentation. Applicant requests that the Examiner withdraw the rejection.

CONCLUSIONS

Applicant submits that all grounds for rejection have been overcome, and that all claims are now in condition for allowance, which action is requested.

Attached is a marked-up version of the changes being made by the current amendments. The attached pages are captioned "Version with Markings to Show Changes Made."

Enclosed is a Petition for Extension of Time and a $110 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 07334-142001.

Respectfully submitted,

Date: November 12, 2002

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Version with Markings to Show Changes Made

In the Claims:

Claims 9-20 have been cancelled.

Pending Claims

1. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO:2.

2. The isolated polypeptide of claim 1, wherein the polypeptide consists of the amino acid sequence of SEQ ID NO:2.

3. An isolated polypeptide comprising at least 25 contiguous amino acids of the amino acid sequence of SEQ ID NO:2.

4. The isolated polypeptide of claim 3, wherein the polypeptide comprises at least 50 contiguous amino acids of the amino acid sequence of SEQ ID NO:2.

5. The isolated polypeptide of claim 3, wherein the polypeptide comprises at least 100 contiguous amino acids of the amino acid sequence of SEQ ID NO:2.

6. The isolated polypeptide of claim 3, wherein the polypeptide comprises at least 200 contiguous amino acids of the amino acid sequence of SEQ ID NO:2.

7. The isolated polypeptide of claim 3, wherein the polypeptide comprises at least 400 contiguous amino acids of the amino acid sequence of SEQ ID NO:2.

8. The isolated polypeptide of claim 3, wherein the polypeptide comprises at least 600 contiguous amino acids of the amino acid sequence of SEQ ID NO:2.

21. The polypeptide of claim 3 comprising amino acids 10-116 of SEQ ID NO:2.

22. The polypeptide of claim 3 comprising amino acids 126-420 of SEQ ID NO:2.

23. The polypeptide of claim 3 comprising amino acids 568-660 of SEQ ID NO:2.

24. The polypeptide of claim 3 comprising amino acids 676-745 of SEQ ID NO:2.

25. The polypeptide of claim 3 comprising amino acids 826-1004 of SEQ ID NO:2.

26. A polypeptide comprising an amino acid sequence that is at least 85% identical to the sequence of SEQ ID NO:2, wherein the polypeptide binds to Bcl-10.

27. The polypeptide of claim 26, wherein the amino acid sequence is at least 95% identical to the sequence of SEQ ID NO:2.

28. The polypeptide of claim 26, wherein the amino acid sequence is at least 98% identical to the sequence of SEQ ID NO:2.

29. A polypeptide comprising an amino acid sequence that is at least 85% identical to the sequence of SEQ ID NO:2, wherein the polypeptide activates NF-kB.

30. The polypeptide of claim 29, wherein the amino acid sequence is at least 95% identical to the sequence of SEQ ID NO:2.

31. The polypeptide of claim 29, wherein the amino acid sequence is at least 98% identical to the sequence of SEQ ID NO:2.

32. A fusion protein comprising the polypeptide of claim 1 linked by a peptide bond to a heterologous polypeptide.

33. A fusion protein comprising the polypeptide of claim 3 linked by a peptide bond to a heterologous polypeptide.

34. A fusion protein comprising the polypeptide of claim 21 linked by a peptide bond to a heterologous polypeptide.